

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Intellectual Application of: Judith A. Varner *et al.*
Serial No.: 10/518,181
371 Date: 09/09/2005
Entitled: **Methods for Inhibiting Angiogenesis, Cell Migration, Cell Adhesion, and Cell Survival**

Group No.: 1633
Examiner: Nguyen, Q.

INFORMATION DISCLOSURE STATEMENT

MS Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: September 5, 2007

By: 

Cliff Cannon-Cin

Dear Sir or Madam:

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. § 1.56 and § 1.97. The Examiner is requested to make these citations of official record in this application.

The following citations are referred to in the body of the Specification:

- Abou-Samra *et al.*, "Expression cloning of a common receptor for parathyroid hormone and parathyroid hormone-related peptide from rat osteoblast-like cells: a single receptor stimulates intracellular accumulation of both cAMP and inositol trisphosphates and increases intracellular free calcium," *Proc Natl Acad Sci USA*, 89: 2732-2736 (1992);
- Amizuka *et al.*, "Parathyroid hormone-related peptide-depleted mice show abnormal epiphyseal cartilage development and altered endochondral bone formation," *J Cell Biol*, 126: 1611-1623 (1994);

- Arap *et al.*, "Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model," *Science*, 279: 377-380 (1998);
- Ausprunk *et al.*, "Vascularization of normal and neoplastic tissues grafted to the chick chorioallantois. Role of host and preexisting graft blood vessels," *Amer J Pathol*, 79:597-628 (1975);
- Bakre *et al.*, "Parathyroid hormone related peptide is a naturally occurring protein kinase A-dependent angiogenesis inhibitor," *Nature Med*, 8: 995-1003 (2002);
- Boudreau *et al.*, "Suppression of ICE and apoptosis in mammary epithelial cells by extracellular matrix," *Science*, 267: 891-893 (1995);
- Brooks *et al.*, "Integrin alpha-v/beta-3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels," *Cell*, 79: 1157-1164 (1994) abstract;
- Brooks *et al.*, "Requirement of vascular integrin alpha-v/beta-3 for angiogenesis," *Science*, 264: 569-571 (1994);
- Bukoski *et al.*, "Vascular actions of the calcium-regulating hormones," *Semin Nephrol*, 15: 536-549 (1995) abstract;
- Carmeliet and Jain, "Angiogenesis in cancer and disease," *Nature*, 407: 249-257 (2000);
- Carron *et al.*, "A peptidomimetic antagonist of the integrin alpha-v/beta-3 inhibits Leydig cell tumor growth and the development of hypercalcemia of malignancy," *Cancer Res*, 58: 1930-1955 (1998);
- Christofidou-Solomidou *et al.*, "Expression and function of endothelial cell alpha-v integrin receptors in wound-induced human angiogenesis in human skin/SCID mice chimeras," *Am J Pathol*, 151: 975-983 (1997);
- Clark *et al.*, "Transient functional expression of alpha-v/beta-3 on vascular cells during wound repair," *Am J Pathol*, 148: 1407-1421 (1996);
- Clegg *et al.*, "Inhibition of intracellular cAMP-dependent protein kinase using mutant genes of the regulatory type I subunit," *J Biol Chem*, 262: 13111-13119 (1987);
- Dormond *et al.*, "NSAIDs inhibit alpha-v/beta-3 integrin-mediated and Cdc42/Rac-dependent endothelial-cell spreading, migration and angiogenesis," *Nat Med*, 7: 1041-1047 (2001);

- Drake *et al.*, "An antagonist of integrin alpha-v/beta-3 prevents maturation of blood vessels during embryonic neovascularization," J Cell Science, 108: 2655-2661 (1995);
- Elicieri and Cheresch, "The role of alpha-v integrins during angiogenesis: insights into potential mechanisms of action and clinical development," J Clin Invest, 103: 1227-1230 (1999);
- Friedlander *et al.*, "Definition of two angiogenic pathways by distinct alpha-v integrins," Science, 270: 1500-1502 (1995);
- Friedlander *et al.*, "Involvement of integrins alpha-v/beta-3 and alpha-v/beta-5 in ocular neovascular diseases," Proc Natl Acad Sci USA, 93: 9764-9769 (1996);
- Grant *et al.*, "Two different laminin domains mediate the differentiation of human endothelial cells into capillary-like structures in vitro," Cell, 58:933-943 (1989) abstract;
- Guise *et al.*, "Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis," J Clin Invest, 98: 1544-1549 (1996);
- Gujral *et al.*, "Parathyroid hormone-related protein induces interleukin-8 production by prostate cancer cells via a novel intracrine mechanism not mediated by its classical nuclear localization sequence," Cancer Res, 61: 2282-2288 (2001);
- Hoare *et al.*, "Evaluating the signal transduction mechanism of the parathyroid hormone 1 receptor. Effect of receptor-G-protein interaction on the ligand binding mechanism and receptor conformation," J Biol Chem, 276: 7741-7753 (2001);
- Howe and Juliano, "Regulation of anchorage-dependent signal transduction by protein kinase A and p21-activated kinase," Nat Cell Biol, 2: 593-600 (2000) abstract;
- Humphries *et al.*, "A synthetic peptide from fibronectin inhibits experimental metastasis of murine melanoma cells," Science, 233:467-470 (1986);
- Humphries *et al.*, "Investigation of the biological effects of anti-cell adhesive synthetic peptides that inhibit experimental metastasis of B16-F10 murine melanoma cells," J Clin Invest, 81:782-790 (1988);
- Isner and Asahara, "Angiogenesis and vasculogenesis as therapeutic strategies for postnatal neovascularization," J Clin Invest, 103:1231-1236 (1999);

- Iwamoto *et al.*, "Changes in parathyroid hormone receptors during chondrocyte cytodifferentiation," J Biol Chem, 269: 17245-17251 (1994);
- Jiang *et al.*, "Expression of parathyroid hormone/parathyroid hormone-related protein receptor in vascular endothelial cells," J Cardiovascular Pharmacol, S142-1444 (1998) abstract;
- Jin *et al.*, "Crystal structure of human parathyroid hormone 1-34 at 0.9-A resolution," J Biol Chem, 275: 27238-27244 (2000);
- Karaplis *et al.*, "Lethal skeletal dysplasia from targeted disruption of the parathyroid hormone-related peptide gene," Genes Dev, 8: 277-289 (1994);
- Kim *et al.*, "Regulation of angiogenesis in vivo by ligation of integrin alpha-5/beta-1 with the central cell-binding domain of fibronectin," Am J Pathol, 156:1345-1362 (2000);
- Kim *et al.*, "Regulation of integrin alpha-v/beta-3-mediated endothelial cell migration and angiogenesis by integrin alpha-5/beta-1 and protein kinase A," J Biol Chem, 275: 33920-33928 (2000);
- Kiosses *et al.*, "A role for p21-activated kinase in endothelial cell migration," J Cell Biol, 147: 831-843 (1999);
- Kiosses *et al.*, "Rac recruits high-affinity integrin alpha-v/beta-3 to lamellipodia in endothelial cell migration," Nat Cell Biol, 3: 316-320 (2001) abstract;
- Kjoller and Hall, "Rac mediates cytoskeletal rearrangements and increased cell motility induced by urokinase-type plasminogen activator receptor binding to vitronectin," J Cell Biol, 152: 1145-1157 (2001);
- Kumar *et al.*, "Targeting integrins alpha-5/beta-3 and alpha-5/beta-5 for blocking tumor-induced angiogenesis" in Maragoudakis (ed.), Advances in Experimental Medicine and Biology, (Angiogenesis: From the Molecular to Integrative Pharmacology), Kluwer Academic / Plenum Publishers: New York, 476:169-180 (2000);
- Lanske *et al.*, "Ablation of the PTHrP gene or the PTH/PTHrP receptor gene leads to distinct abnormalities in bone development," J Clin Invest, 104: 399-407 (1999);
- Leavesley *et al.*, "Integrin beta-1 and beta-3 mediated endothelial cell migration is triggered through distinct signaling mechanisms," J Cell Biol, 121: 163-170 (1993);


- Maeda *et al.*, "Targeted overexpression of parathyroid hormone-related protein (PTHrP) to vascular smooth muscle in transgenic mice lowers blood pressure and alters vascular contractility," *Endocrinology*, 140: 1815-1825 (1999);
- Meredith Jr. *et al.*, "The extracellular matrix as a cell survival factor," *Mol Biol Cell*, 4: 953-961 (1993);
- Ossowski and Reich, "Experimental model for quantitative study of metastasis," *Cancer Res*, 40:2300-2309 (1980);
- Penta *et al.*, "Dell induces integrin signaling and angiogenesis by ligation of alpha-v/beta-3," *J Biol Chem*, 274: 11101-11109 (1999);
- Shimizu *et al.*, "Minimization of parathyroid hormone. Novel amino-terminal parathyroid hormone fragments with enhanced potency in activating the type-1 parathyroid hormone receptor," *J Biol Chem*, 275: 21836-218343 (2000);
- Sipkins *et al.*, "Detection of tumor angiogenesis in vivo by alpha-v/beta-3 targeted magnetic resonance imaging," *Nat Med*, 4: 623-626 (1998);
- Stromblad *et al.*, "Suppression of p53 activity and p21 WAF1/CIP1 expression by vascular cell integrin alpha-v/beta-3 during angiogenesis," *J Clin Invest*, 98: 426-433 (1996);
- Takahashi *et al.*, "Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization," *Nat Med*, 5:434-438 (1999);
- Terkeltaub *et al.*, "Parathyroid hormone-related proteins is abundant in osteoarthritic cartilage, and the parathyroid hormone-related protein 1-173 isoform is selectively induced by transforming growth factor beta in articular chondrocytes and suppresses generation of extracellular inorganic pyrophosphate," *Arthritis Rheum*, 41: 2152-64 (1998);
- Varner *et al.*, "Inhibition of angiogenesis and tumor growth by murine 7E3, the parent antibody of C7E3 fab (abciximab; ReoPro)," *Angiogenesis*, 3:53-60 (1999);
- GenBank Accession No. NM_000315 (PTH);
- GenBank Accession No. NM_002820 (PTHrP); and
- GenBank Accession No NM_008854 (PKA).

The following citations, copies attached, were cited during examination of the parent PCT Application No. PCT/US03/20041 (UCSD-07947):

- Kim *et al.*, "Inhibition of endothelial cell survival and angiogenesis by protein kinase A," J Clin Invest, 110: 933-941 (2002);
- Romano *et al.*, "Latest developments in gene transfer technology: achievements, perspectives, and controversies over therapeutic applications," Stem Cells, 18: 19-39 (2000); and
- Shepard, "Endothelial integrins and angiogenesis: not so simple anymore," J Clin Invest, 110: 913-914 (2002).

This Information Disclosure Statement under 37 C.F.R. § 1.56 and § 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: September 5, 2007

By: 
Christine A. Lekutis
Registration No. 51,934

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
415.904.6500

FORM PTO-1449
(Modified)U.S. Department of Commerce
Patent and Trademark Office

Attorney Docket No. CSD-08879

Serial No.: 10/518,181

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(37 CFR § 1.98(b))

Applicant: Judith A. Varner et al.

Filing or 371(c) Date: 09/09/2005

Group Art Unit: 1633

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	Document / Patent Number	Publication / Issue Date	Applicant / Patentee	Class	Subclass	Filing Date

FOREIGN PATENTS OR PUBLISHED FOREIGN PATENT APPLICATIONS

Document Number	Publication Date	Country / Patent Office	Class	Subclass	Translation	
					Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Relevant Pages, Place of Publication)

1	Abou-Samra <i>et al.</i> , "Expression cloning of a common receptor for parathyroid hormone and parathyroid hormone-related peptide from rat osteoblast-like cells: a single receptor stimulates intracellular accumulation of both cAMP and inositol trisphosphates and increases intracellular free calcium," Proc Natl Acad Sci USA, 89: 2732-2736 (1992)
2	Amizuka <i>et al.</i> , "Parathyroid hormone-related peptide-depleted mice show abnormal epiphyseal cartilage development and altered endochondral bone formation," J Cell Biol, 126: 1611-1623 (1994)
3	Arap <i>et al.</i> , "Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model," Science, 279: 377-380 (1998)
4	Ausprunk <i>et al.</i> , "Vascularization of normal and neoplastic tissues grafted to the chick chorioallantois. Role of host and preexisting graft blood vessels," Amer J Pathol, 79:597-628 (1975)
5	Bakre <i>et al.</i> , "Parathyroid hormone related peptide is a naturally occurring protein kinase A-dependent angiogenesis inhibitor," Nature Med, 8: 995-1003 (2002)
6	Boudreau <i>et al.</i> , "Suppression of ICE and apoptosis in mammary epithelial cells by extracellular matrix," Science, 267: 891-893 (1995)
7	Brooks <i>et al.</i> , "Integrin alpha-v/beta-3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels," Cell, 79: 1157-1164 (1994) abstract
8	Brooks <i>et al.</i> , "Requirement of vascular integrin alpha-v/beta-3 for angiogenesis," Science, 264: 569-571 (1994)
9	Bukoski <i>et al.</i> , "Vascular actions of the calcium-regulating hormones," Semin Nephrol, 15: 536-549 (1995) abstract
10	Carmeliet and Jain, "Angiogenesis in cancer and disease," Nature, 407: 249-257 (2000)
11	Carron <i>et al.</i> , "A peptidomimetic antagonist of the integrin alpha-v/beta-3 inhibits Leydig cell tumor growth and the development of hypercalcemia of malignancy," Cancer Res, 58: 1930-1955 (1998)
12	Christofidou-Solomidou <i>et al.</i> , "Expression and function of endothelial cell alpha-v integrin receptors in wound-induced human angiogenesis in human skin/SCID mice chimeras," Am J Pathol, 151: 975-983 (1997)
13	Clark <i>et al.</i> , "Transient functional expression of alpha-v/beta-3 on vascular cells during wound repair," Am J Pathol, 148: 1407-1421 (1996)
14	Clegg <i>et al.</i> , "Inhibition of intracellular cAMP-dependent protein kinase using mutant genes of the regulatory type I subunit," J Biol Chem, 262: 13111-13119 (1987)
15	Dormond <i>et al.</i> , "NSAIDs inhibit alpha-v/beta-3 integrin-mediated and Cdc42/Rac-dependent endothelial-cell spreading, migration and angiogenesis," Nat Med, 7: 1041-1047 (2001)
16	Drake <i>et al.</i> , "An antagonist of integrin alpha-v/beta-3 prevents maturation of blood vessels during embryonic neovascularization," J Cell Science, 108: 2655-2661 (1995)
17	Elicieri and Cheresch, "The role of alpha-v integrins during angiogenesis: insights into potential mechanisms of action and clinical development," J Clin Invest, 103: 1227-1230 (1999)
18	Friedlander <i>et al.</i> , "Definition of two angiogenic pathways by distinct alpha-v integrins," Science, 270: 1500-1502 (1995)
19	Friedlander <i>et al.</i> , "Involvement of integrins alpha-v/beta-3 and alpha-v/beta-5 in ocular neovascular diseases," Proc Natl Acad Sci USA, 93: 9764-9769 (1996)
20	Grant <i>et al.</i> , "Two different laminin domains mediate the differentiation of human endothelial cells into capillary-like structures in vitro," Cell, 58:933-943 (1989) abstract
21	Guise <i>et al.</i> , "Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis," J Clin Invest, 98: 1544-1549 (1996)
22	Gujral <i>et al.</i> , "Parathyroid hormone-related protein induces interleukin-8 production by prostate cancer cells via a novel intracrine mechanism not mediated by its classical nuclear localization sequence," Cancer Res, 61: 2282-2288 (2001)
23	Hoare <i>et al.</i> , "Evaluating the signal transduction mechanism of the parathyroid hormone 1 receptor. Effect of receptor-G-protein interaction on the ligand binding mechanism and receptor conformation," J Biol Chem, 276: 7741-7753 (2001)
24	Howe and Juliano, "Regulation of anchorage-dependent signal transduction by protein kinase A and p21-activated kinase," Nat Cell Biol, 2: 593-600 (2000) abstract
25	Humphries <i>et al.</i> , A synthetic peptide from fibronectin inhibits experimental metastasis of murine melanoma cells," Science, 233:467-470 (1986)

Examiner:

Date Considered:

EXAMINER:Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. JCSD-08879	Serial No.: 10/518,181
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (37 CFR § 1.98(b))				Applicant: Judith A. Varner et al.	
				Filing or 371(c) Date: 09/09/2005	Group Art Unit: 1633
OTHER DOCUMENTS (Including Author, Title, Date, Relevant Pages, Place of Publication)					
	26	Humphries <i>et al.</i> , "Investigation of the biological effects of anti-cell adhesive synthetic peptides that inhibit experimental metastasis of B16-F10 murine melanoma cells," J Clin Invest, 81:782-790 (1988)			
	27	Isner and Asahara, "Angiogenesis and vasculogenesis as therapeutic strategies for postnatal neovascularization," J Clin Invest, 103:1231-1236 (1999)			
	28	Iwamoto <i>et al.</i> , "Changes in parathyroid hormone receptors during chondrocyte cytodifferentiation," J Biol Chem, 269: 17245-17251 (1994)			
	29	Jiang <i>et al.</i> , "Expression of parathyroid hormone/parathyroid hormone-related protein receptor in vascular endothelial cells," J Cardiovascular Pharmacol, S142-1444 (1998) abstract			
	30	Jin <i>et al.</i> , "Crystal structure of human parathyroid hormone 1-34 at 0.9-A resolution," J Biol Chem, 275: 27238-27244 (2000)			
	31	Karaplis <i>et al.</i> , "Lethal skeletal dysplasia from targeted disruption of the parathyroid hormone-related peptide gene," Genes Dev, 8: 277-289 (1994)			
	32	Kim <i>et al.</i> , "Regulation of angiogenesis in vivo by ligation of integrin alpha-5/beta-1 with the central cell-binding domain of fibronectin," Am J Pathol, 156:1345-1362 (2000)			
	33	Kim <i>et al.</i> , "Regulation of integrin alpha-v/beta-3-mediated endothelial cell migration and angiogenesis by integrin alpha-5/beta-1 and protein kinase A," J Biol Chem, 275: 33920-33928 (2000)			
	34	Kiosses <i>et al.</i> , "A role for p21-activated kinase in endothelial cell migration," J Cell Biol, 147: 831-843 (1999)			
	35	Kiosses <i>et al.</i> , "Rac recruits high-affinity integrin alpha-v/beta-3 to lamellipodia in endothelial cell migration," Nat Cell Biol, 3: 316-320 (2001) abstract			
	36	Kjoller and Hall, "Rac mediates cytoskeletal rearrangements and increased cell motility induced by urokinase-type plasminogen activator receptor binding to vitronectin," J Cell Biol, 152: 1145-1157 (2001)			
	37	Kumar <i>et al.</i> , "Targeting integrins alpha-5/beta-3 and alpha-5/beta-5 for blocking tumor-induced angiogenesis" in Maragoudakis (ed.), <u>Advances in Experimental Medicine and Biology</u> , (Angiogenesis: From the Molecular to Integrative Pharmacology), Kluwer Academic / Plenum Publishers: New York, 476:169-180 (2000)			
	38	Lanske <i>et al.</i> , "Ablation of the PTHrP gene or the PTH/PTHrP receptor gene leads to distinct abnormalities in bone development," J Clin Invest, 104: 399-407 (1999)			
	39	Leavesley <i>et al.</i> , "Integrin beta-1 and beta-3 mediated endothelial cell migration is triggered through distinct signaling mechanisms," J Cell Biol, 121: 163-170 (1993)			
	40	Maeda <i>et al.</i> , "Targeted overexpression of parathyroid hormone-related protein (PTHrP) to vascular smooth muscle in transgenic mice lowers blood pressure and alters vascular contractility," Endocrinology, 140: 1815-1825 (1999)			
	41	Meredith Jr. <i>et al.</i> , "The extracellular matrix as a cell survival factor," Mol Biol Cell, 4: 953-961 (1993)			
	42	Ossowski and Reich, "Experimental model for quantitative study of metastasis," Cancer Res, 40:2300-2309 (1980)			
	43	Penta <i>et al.</i> , "Dell induces integrin signaling and angiogenesis by ligation of alpha-v/beta-3," J Biol Chem, 274: 11101-11109 (1999)			
	44	Shimizu <i>et al.</i> , "Minimization of parathyroid hormone. Novel amino-terminal parathyroid hormone fragments with enhanced potency in activating the type-1 parathyroid hormone receptor," J Biol Chem, 275: 21836-218343 (2000)			
	45	Sipkins <i>et al.</i> , "Detection of tumor angiogenesis in vivo by alpha-v/beta-3 targeted magnetic resonance imaging," Nat Med, 4: 623-626 (1998)			
	46	Stromblad <i>et al.</i> , "Suppression of p53 activity and p21WAF1/CIP1 expression by vascular cell integrin alpha-v/beta-3 during angiogenesis," J Clin Invest, 98: 426-433 (1996)			
	47	Takahashi <i>et al.</i> , "Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization," Nat Med, 5:434-438 (1999)			
	48	Terkeltaub <i>et al.</i> , "Parathyroid hormone-related proteins is abundant in osteoarthritic cartilage, and the parathyroid hormone-related protein 1-173 isoform is selectively induced by transforming growth factor beta in articular chondrocytes and suppresses generation of extracellular inorganic pyrophosphate," Arthritis Rheum, 41: 2152-64 (1998)			
	49	Varner <i>et al.</i> , "Inhibition of angiogenesis and tumor growth by murine 7E3, the parent antibody of C7E3 fab (abciximab; ReoPro)," Angiogenesis, 3:53-60 (1999)			
	50	GenBank Accession No. NM_000315 (PTH)			
	51	GenBank Accession No. NM_002820 (PTHrP)			
	52	GenBank Accession No NM_008854 (PKA)			
	53	Kim <i>et al.</i> , "Inhibition of endothelial cell survival and angiogenesis by protein kinase A," J Clin Invest, 110: 933-941 (2002)			
	54	Romano <i>et al.</i> , "Latest developments in gene transfer technology: achievements, perspectives, and controversies over therapeutic applications," Stem Cells, 18: 19-39 (2000)			
	55	Shepard, "Endothelial integrins and angiogenesis: not so simple anymore," J Clin Invest, 110: 913-914 (2002)			
Examiner:			Date Considered:		
EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.					